Effects of the opioid remifentanil on the arrhythmogenicity of epinephrine in halothane-anesthetized dogs

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Abstract

Opioids may exert a protective effect against ventricular arrhythmias via a vagally mediated mechanism. This study evaluated the effects of the opioid remifentanil on arrhythmogenicity of epinephrine during halothane anesthesia. Eight dogs were assigned to 2 treatments in a randomized crossover design, with 1-week intervals between treatments. Anesthesia was maintained with 1.3% end-tidal halothane in oxygen and mechanical ventilation to maintain eucapnia. A constant rate infusion of remifentanil (0.72 μg/kg/min) was administered throughout the study in the experimental treatment, while control animals received physiologic saline as placebo. The arrhythmogenic dose of epinephrine (ADE), defined as 4 premature ventricular complexes (PVCs) within 15 s, was determined by administering progressively increasing infusion rates of epinephrine (2.5, 5.0, and 10 μg/kg/min), allowing 20 min intervals between each infusion rate. In both treatments, epinephrine infusions induced bradyarrhythmias and atrioventricular conduction disturbances, which were followed by escape beats and PVCs. In the remifentanil treatment, mean ± *s* ADE values (11.3 ± 4.9 μg/kg) did not differ from values observed in control animals (9.9 ± 6.1 μg/kg). On the basis of the ADE model for assessing the arrhythmogenity of drugs during halothane anesthesia, the present study did not demonstrate a protective effect of remifentanil (0.72 μg/kg/min) against ventricular arrhythmias in dogs.

Résumé

Les opioïdes peuvent avoir un effet protecteur contre les arythmies ventriculaires via un mécanisme à médiation vagale. La présente étude visait à évaluer les effets de l'opioïde remifentanil sur l'effet arythmogénique de l'adrénaline durant une anesthésie à l'halothane. Huit chiens ont été assignés à 2 traitements selon un design expérimental croisé avec répartition au hasard, avec un intervalle de 1 semaine entre les traitements. L'anesthésie a été maintenue avec une concentration télo-expiratoire de 1,3 % d'halothane dans de l'oxygène et ventilation mécanique afin de maintenir l'eucapnée. Un taux constant d'infusion de remifentanil (0,72 μg/kg/min) a été administré tout au long de l'étude pour le groupe avec traitement expérimental, alors que les animaux témoins recevaient de la saline physiologique à titre de placebo. La dose d'adrénaline ayant un effet arythmogénique (ADE), définie comme étant celle causant 4 complexes ventriculaires prématurés (PVCs) en moins de 15 s, a été déterminée en administrant de manière progressive des taux croissants d'adrénaline en infusion (2,5, 5,0 et 10 μg/kg/min), avec des intervalles de 20 min entre chaque taux d'infusion. Lors des deux traitements, les infusions d'adrénaline ont induit de la brady-arythmie et des interférences dans la conduction atrio-ventriculaire, qui ont été suivies par des battements échappés et des PVCs. Lors du traitement avec le remifentanil, les valeurs moyennes ± s d'ADE (11,3 ± 4,9 μg/kg) ne différaient pas des valeurs observées pour les animaux témoins (9,9 ± 6,1 μg/kg). Basé sur le modèle de l'ADE pour évaluer l'effet arythmogène de drogues durant une anesthésie à l'halothane, la présente étude n'a pas permis de démontrer un effet protecteur pour le remifentanil (0,72 μg/kg,min) contre l'arythmie ventriculaire chez les chiens.

(Traduit par Docteur Serge Messier)

Introduction

Intraoperative arrhythmias are a concern during anesthesia, and selection of anesthetic technique should emphasize the use of drugs that minimize the occurrence of potentially fatal ventricular arrhythmias. Although retrospective studies in the veterinary literature are lacking, perioperative arrhythmias were reported to occur in 20% to 50% of human patients (1). The arrhythmogenic potential of anesthetic drugs has been assessed on the basis of the arrhythmogenic dose of epinephrine (ADE) model, where epinephrine is administered at progressively increasing infusion rates until a pre-defined ventricular arrhythmia criterion is met (2,3). Comparison between anesthetics regarding their arrhythmogenicity (capacity to predispose to ventricular arrhythmias) is then performed by comparison between ADE values. A drug or anesthetic regimen is considered more arrhythmogenic if ADE decreases in comparison to a control and vice-versa (3). The phenothiazine derivatives (acepromazine) and butyrophenones (droperidol) are recognized as anti-arrhythmogenic

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agents since previous administration of these drugs cause an increase in the dose of epinephrine necessary to induce ventricular premature depolarizations (VPCs) (4,5).

Opioids are widely used in balanced anesthesia techniques. In conscious and in anesthetized dogs, the opioid morphine decreases the risk of ventricular fibrillation, which is a terminal event that may follow VPCs (6,7). Evidence for an anti-arrhythmogenic effect of morphine in these previous studies was provided by the repetitive extrasystole threshold method (6–8). In this methodology, repetitive extrasystoles (VPCs) are induced by a constant current stimulator implanted in the right ventricle, and an increase in the amount of electrical current necessary to induce repetitive extrasystoles in comparison to a control provides evidence for an anti-arrhythmogenic effect (8). The short acting opioid fentanyl (30 μg/kg) protected the heart against ventricular fibrillation in dogs anesthetized with alpha-chloralose as shown by increased amount of electrical current applied to the right ventricle that induced ventricular fibrillation (9). In conscious rats, morphine administration increased the amount of epinephrine necessary to induce VPCs and cardiac arrest, apparently via a mechanism dependent on the action of the opioid on brain mu receptors (10).

In spite of evidence showing that opioids may protect the heart against ventricular arrhythmias, to our knowledge, there are no published studies using the ADE methodology for assessing anti-arrhythmogenic potential of the opioid remifentanil in halothane anesthetized dogs. The mu opioid agonist remifentanil approaches the ideal profile of an injectable agent suitable for a continuous infusion regimen (11). This opioid has a very rapid onset and offset of action as metabolism occurs via nonspecific esterases (11). In man and in dogs remifentanil results in fast recoveries and relatively stable plasma levels during maintenance of a constant rate infusion (11,12). We hypothesized that remifentanil exerts a protective effect against epinephrine induced ventricular premature depolarizations during halothane anesthesia.

Materials and methods

Animals and study design

This study was approved by the Institutional Animal Care Committee (protocol 138-06 CEEA). Eight healthy spayed adult female dogs (weight 15.4 ± 2.3 kg) were used in a randomized crossover design. Each dog received 2 treatments (control and remifentanil) with a minimum of 1-wk interval between experiments. Health status was based on physical examination, complete blood (cell) count, electrocardiography, and blood gas analysis.

Experimental protocol

Anesthesia was induced with 5% halothane (Halotano; Cristália, Itapira, SP, Brazil) in oxygen delivered by a facemask attached to a circle breathing system (Conquest 3000; HB Hospitalar, São Paulo, SP, Brazil). After endotracheal tube placement, vaporizer settings were adjusted to maintain end-tidal halothane concentrations at 1.3% in both treatments. An infrared gas analyzer (Gas analyzer module G-AO; Datex-Ëngstrom, Helsinki, Finland) calibrated with a standard gas mixture containing 5% carbon dioxide (CO_2), 55% oxygen (O_2), 33% nitrous oxide (N_2O), and 3% anesthetic agent (Quick Cal Calibration Gas; Datex-Ëngstrom, Helsinki, Finland) was connected to the distal end of the endotracheal tube to allow continuous monitoring of end-tidal halothane concentrations. Inspiratory positive pressure ventilation (Conquest 3000, HB Hospitalar) was employed throughout the study (peak inspiratory pressure of 8 to 15 cm H_2O, inspiration-to-expiration ratio of 1:2, and respiratory rate between 8 to 18 breaths/min) aiming to maintain arterial CO_2 tension ($PaCO_2$) between 35 and 40 mm Hg. To ensure that $PaCO_2$ values were within the reference ranges, arterial blood gases were measured (pH/Blood Gas Analyzer Model 348; Chiron Diagnostics, Halstead, UK) at least 2 times between epinephrine infusions for ADE determination; ventilatory parameters were further adjusted in order to achieve the desired $PaCO_2$ range as needed. Throughout the study, esophageal temperature was maintained between 37.0 and 38.5°C by means of a forced warm air blanket (Warmtouch; Mallinkrodt Medical, Pleasanton, California, USA).

A 20-gauge catheter (Insyte; Becton-Dickinson, Sandy, Utah, USA) was placed in the cephalic vein for drug administration and for fluid therapy with Lactated Ringer's solution administered at 5 mL/kg/h by means of an infusion pump (LF 2001; Lifemed, São Paulo, SP, Brazil). Adhesive electrodes were placed on the skin to monitor lead II electrocardiogram (ECG), while systolic, diastolic, and mean arterial pressure (SAP, DAP and MAP) values where monitored via a fluid-filled pressure transducer (model PX260; Baxter Healthcare Corp, Irving, California, USA) connected to an 18-gauge catheter (Insyte; Becton-Dickinson) placed in the femoral artery. Accuracy of the pressure transducer was previously checked with a mercury column prior to each experiment.

In the control treatment, anesthesia was maintained with halothane and a constant rate infusion of physiologic saline (placebo), whereas in the experimental treatment anesthesia was maintained with halothane and a constant rate infusion of remifentanil (0.72 μg/kg/min). Infusion treatments were administered by means of a syringe pump (ST 680; Samtronic, São Paulo, SP, Brazil). The same end-tidal halothane concentration (1.3%) was used in both treatments; also, the infusion rates (mL/kg/min) administered intravenously (physiologic saline or remifentanil) were the same regardless of the treatment group.

A period of 60 min of constant end-tidal halothane (1.3%) was allowed prior to determining ADE values. Epinephrine was administered at progressively higher infusion rates (2.5, 5.0, and 10.0 μg/kg/min) by means of a peristaltic infusion pump (LF 2001; Lifemed, São Paulo, SP, Brazil), until achieving a pre-defined arrhythmia criterion (13). Each infusion rate was maintained for 3 min, with 20-min intervals between infusions. When the ventricular arrhythmia criterion was observed on the ECG tracing, epinephrine infusion was immediately interrupted and a lidocaine bolus (2 mg/kg, IV) was administered to prevent arrhythmia progression to ventricular fibrillation.

Since prolonged epinephrine administration may cause an increase in base deficit due to vasoconstriction leading to impaired peripheral perfusion, eventual reductions in bicarbonate levels $<$ 19 mEq/L were treated by administering IV boluses of sodium bicarbonate (0.2 mEq/kg) until arterial bicarbonate levels were within reference ranges (19 to 24 mEq/L).

Table I. Cardiovascular variables observed before starting the infusion rate where the ADE criterion was met (baseline) and immediately prior to the moment where the first VPC that met ADE criterion (ADE) was observed in 8 halothane anesthetized dogs receiving a constant rate infusion of physiologic saline (control) or remifentanil (0.72 μg/kg/min)

		Baseline	ADE
HR (beats/min)	Control	81 ± 12	49 ± 10^{a}
	Remifentanil	74 ± 15^{b}	61 ± 18
SAP (mm Hg)	Control	126 ± 21	283 ± 12^{a}
	Remifentanil	107 ± 11	274 ± 23^{a}
DAP (mm Hg)	Control	73 ± 17	164 ± 12^{a}
	Remifentanil	52 ± 10^{b}	169 ± 12^{a}
MAP (mm Hg)	Control	88 ± 18	196 ± 8^{a}
	Remifentanil	67 ± 11^{b}	194 ± 15^{a}

Values are presented as mean ± s.
[a] Significant difference from baseline ($P < 0.05$).
[b] Significant difference from Control treatment ($P < 0.05$).

Table II. Incidence (number of animals) of ventricular and supraventricular de arrhythmias observed during the epinephrine infusion where the ADE criterion was observed in 8 halothane anesthetized dogs receiving a constant rate infusion of physiologic saline (control) or remifentanil (0.72 μg/kg/min)

Rhythm	Control	Remifentanil
Bradycardia (HR < 60 bpm)	6	7
Sinus arrhythmia	6	4
Second degree AV block	4	3
Sinus arrest	3	1
Accelerated idioventricular rhythm	2	2
AV dissociation	6	5
Atrial premature complexes	1	—
Ventricular escape beats	5	7
Ventricular escape rhythm	6	6
Ventricular premature complexes	6	6
Bigeminism	1	2
Trigeminism	2	—
Ventricular tachycardia	7	7

The ADE criterion was considered fulfilled after observing at least 4 VPCs within a 15-s period during epinephrine infusion or until 1 min after the end of the infusion. The ECG tracing was printed throughout the procedure for further analysis. The ADE values (μg/kg) where calculated as the time when the first VPC of the series that met the ADE criterion (min) times the infusion rate (μg/kg/min).

Heart rate (HR), SAP, DAP, MAP were recorded prior to starting the infusion rate where the ADE criterion was observed (baseline) and at the time of ADE observation.

At the end of the procedure, the inhalant anesthetic and infusion drugs were discontinued and the dogs were allowed to recover from anesthesia.

Statistical analysis

Data are expressed as mean ± *s*. Mean ADE values and blood gas values recorded prior to starting the epinephrine infusion rate that resulted in the ventricular arrhythmia criterion were compared by means of a paired *t*-test. A two-way analysis of variance (ANOVA) followed by a Bonferroni-adjusted Student's *t*-test was used for comparison of cardiovascular variables obtained between treatments, whereas a paired *t*-test was used to compare cardiovascular data obtained within each group. Differences were considered significant when $P < 0.05$.

Results

There was no significant difference between treatments for pH, $PaCO_2$ and PaO_2 values prior to starting the epinephrine infusion that resulted in ventricular arrhythmias (overall mean ± *s* values: 7.36 ± 0.02, 36 ± 2 mm Hg, and 509 ± 33 mm Hg for pH, $PaCO_2$, and PaO_2, respectively). Arterial bicarbonate was significantly lower in the remifentanil treatment (20.0 ± 0.7 mEq/L) compared with the controls (21.2 ± 1.3 mEq/L).

Cardiovascular variables recorded at baseline and at the time of ADE observation are reported in Table I. Heart rate (HR), MAP, and DAP were significantly lower in the remifentanil treatment at baseline. In the control treatment, HR decreased in comparison with the baseline at the time of ventricular arrhythmia formation. In both treatments SAP, DAP, and MAP increased from baseline at the time of ADE observation.

Overall incidence of supraventricular and ventricular arrhythmias was similar between groups (Table II). Bradycardia (HR < 60 beats/min), sinus arrest, and conduction disturbances (1st and 2nd degree atrioventricular heart blocks) were observed at the beginning of epinephrine infusion in both groups. With the progression of epinephrine infusion, ventricular escape beats and idioventricular rhythm became evident. The arrhythmia criterion was later achieved by observing VPCs, bigeminism, trigeminism, and ventricular tachycardia. No animals progressed to ventricular fibrillation after achieving the ventricular arrhythmia criterion.

Mean ADE values in the remifentanil treatment (11.3 ± 4.9 μg/kg) did not differ from mean ADE values observed in the control treatment (9.1 ± 6.1 μg/kg).

Discussion

In this study, remifentanil resulted in lower HR, MAP, and DAP values prior to the epinephrine infusion that fulfilled the ventricular arrhythmia criterion. Vagally mediated bradycardia is a common feature of opioid agents and may result in reduction in arterial blood pressure during anesthesia (11). Remifentanil was also associated with a statistically significant reduction in bicarbonate levels. However, the clinical relevance of the phenomenon appears to be insignificant, since mean bicarbonate values were within reference ranges (19 to 24 mEq/L) in both treatments, and the difference between mean values was small.

In dogs, a remifentanil infusion rate similar to that used in the present study (0.72 μg/kg/min) was estimated to reduce enflurane minimum alveolar concentration (MAC) by approximately 50% (13). Opioid agents reduce the MAC of inhalant anesthetics and this anesthetic sparing effect may result in an overall improvement in hemodynamic function, providing that opioid-induced bradycardia is reversed by an anticholinergic agent (14). In our study, the same end-tidal halothane concentrations were used in both remifentanil and control treatments. Although one may expect that use of MAC corrected end-tidal anesthetic concentrations could have influenced some of the cardiovascular parameters assessed in the present study (for example, blood pressure), it is not known whether the use of equipotent halothane concentrations could bear an impact on the ADE values recorded in both treatments.

Bradycardia, periods of sinus arrest, and conduction disturbances (1st and 2nd degree AV blocks, atrioventricular dissociation) were coincident with increased arterial blood pressure in both treatments during epinephrine administration, suggesting that vagal tone was increased due to baroreceptor stimulation. With the progression of the catecholamine infusion, ventricular escape beats preceded the VPCs that were present in the form of isolated VPCs, bigeminy, trigeminy, and multiform ventricular tachycardia. In our study, ADE was considered to be achieved after the observation of at least 4 VPCs within a 15-*s* period (5,15). A broader ADE criterion, defined as the observation of at least 4 ectopic ventricular contractions (EVCs), has been reported in the literature (16–19). Although VPCs and ventricular escape beats originate through different mechanisms, both phenomena may be considered as EVCs (19). In the present study, a more specific criterion (VPCs) was used as the end point for ADE determination because a broader criterion (EVCs instead of VPCs) does not allow direct comparison between ADE values observed for different treatments (19).

Based on the ADE method for studying the arrhythmogenicity of drugs during halothane anesthesia, it appears that remifentanil does not have an anti-arrhythmogenic action. However, one should consider that the previous reports showing evidence for an anti-arrhythmogenic effect of other opioids in canine species were performed using different methods for inducing ventricular arrhythmias (6–7). In some of these studies, dogs were either conscious or anesthetized with alpha-chloralose and the anti-arrhythmogemic effect of the opioid morphine was evidenced by an increase in the current threshold necessary to induce VPCs, rather than by an increase in ADE values (6–7). The ventricular fibrillation threshold, measured as the amount of current delivered by a catheter implanted in the right ventricle that induced ventricular fibrillation, was increased by 29% with the use of the mu opioid agonist fentanyl (30 μg/kg, IV) in alpha-chloralose anesthetized dogs after experimentally induced hemorrhage (9). The action of morphine against ventricular arrhythmias in alpha-chloralose anesthetized dogs was apparently mediated via opioid induced changes in vagal tone, since vagotomy or atropine administration abolished the protective effect of the opioid against ventricular arrhythmias (6). However, the hypothesis that the anti-arrhythmogenic effect of mu opioid agonists involves an increase in efferent vagal tone may not apply to all drugs of this class. In dogs anesthetized with alpha-chloralose, muscarinic blockade with atropine did not affect the anti-fibrillatory effect of fentanyl, suggesting that the contribution of vagal efferent activity for the anti-arrhythmogenic effect may vary among mu opioid agonists (9). It appears that the anti-fibrillatory effect of fentanyl in dogs involves both a vagal component (baroreflex) and a decrease in sympathetic tone (9).

We used the model of ADE determination during halothane anesthesia because this is a widely used method for accessing the pro- or anti-arrhythmogenic effects of drugs used during the perianesthetic period (2–5, 15). If 1 drug is to be tested for its anti-arrhythmogenic potential during anesthesia, halothane would be an adequate agent to be used in the experimental model since this drug is known for sensitizing the myocardium to the arrhythmogenic action of catecolamines (2). However, halothane was shown to reduce parasympathetic and sympathetic efferent activity in a dose related fashion (20). Since the anti-arrhythmogenic effects of opioids appears to take place via changes in autonomic balance (6), the inhibitory effect of halothane on autonomic efferent activity may have represented a confounding factor.

In halothane anesthetized dogs, an increase in vagal activity induced by direct electrical stimulation of both vagi increased the dose of epinephrine necessary to induce ventricular fibrillation (21). However, in the same experimental model, morphine premedication (1 mg/kg) did not increase the arrhythmogenic threshold of epinephrine (21). It appears that alpha-chloralose anesthesia does not interfere with the protective effect of opioids against epinephrine-induced ventricular arrhythmias, as morphine (0.1 mg/kg) raised the dose of epinephrine necessary to induce VPCs in a model of ADE determination in alpha-chloralose anesthetized rats (10). Based on these evidences, one may hypothesize that the ADE model used in the present study could have shown an anti-arrhythmogenic effect of remifentanil during alpha-chloralose anesthesia.

In previous studies, the anti-arrhythmogenic effect of the opioid morphine was shown either in conscious dogs or in dogs anesthetized with alpha-chloralose, a hypnotic agent drug that apparently causes minimal interference in autonomic activity (6,7). In spite of the advantages of alpha-chloralose with respect to cardiovascular stability and lack of significant interference in autonomic balance, this hypnotic agent may result in excessively prolonged recoveries from anesthesia and this drug has been recommended as an anesthetic agent suitable only for non-recovery studies in dogs and other laboratory animals (22,23). Otherwise, the volatile agent isoflurane is proven as an adequate drug for maintaining clinical anesthesia in dogs, providing fast and uncomplicated recoveries. Although isoflurane is highly suitable for clinical anesthesia, this agent does not sensitize the myocardium to epinephrine induced arrhythmias and is not the ideal anesthetic in an ADE model for assessing the pro- or anti-arrhythmic effects of drugs.

In summary, the opioid remifentanil did not influence epinephrine-induced ventricular arrhythmias in halothane anesthetized dogs. Although the use of opioids such as remifentanil during inhalant anesthesia offers advantages such as reduction in inhalant anesthetic requirements (13), it apparently does not minimize the arrhythmogenic action of epinephrine during halothane anesthesia.

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